Complete Summary

GUIDELINE TITLE

Use of raltitrexed (Tomudex) in the management of metastatic colorectal carcinoma.

BIBLIOGRAPHIC SOURCE(S)

Gastrointestinal Cancer Disease Site Group. Use of raltitrexed (Tomudex) in the management of metastatic colorectal cancer. Toronto (ON): Cancer Care Ontario (CCO); 2003 Feb [online update]. 16 p. (Practice guideline; no. 2-17). [22 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Metastatic colorectal cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Gastroenterology
Internal Medicine
Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To make recommendations on the use of raltitrexed (Tomudex) in the treatment of metastatic colorectal cancer

TARGET POPULATION

Adult patients with metastatic colorectal cancer for whom chemotherapy is indicated

INTERVENTIONS AND PRACTICES CONSIDERED

1. 5-fluorouracil plus leucovorin
2. Raltitrexed (Tomudex)

MAJOR OUTCOMES CONSIDERED

- Survival
- Progression-free survival
- Response rate
- Toxicity
- Symptom improvement
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

1998 Guideline

A MEDLINE, CANCERLIT and Cochrane Library (1997, Issue 4) search was done from January 1988 to April 1998 using the terms "colorectal cancer," "colon neoplasms," "rectal neoplasms," "randomized controlled trials," "raltitrexed" and "Tomudex." Information provided by Zeneca Inc. was also used. The current report, however, relies mostly on clinical trials which have been published either in full or abstract form. The Physicians Data Query (PDQ) database was searched to find ongoing trials (both those that are actively accruing patients and those that have recently closed).

2003 Update

Entries to MEDLINE (through to February [week 2] 2003), CANCERLIT (through to October 2002) and Cochrane Library (through to Issue 4, 2002) databases and abstracts published in the proceedings of the 1999 through 2002 annual meetings of the American Society of Clinical Oncology have been searched for evidence relevant to this practice guideline. The Physician Data Query (PDQ) database of

ongoing clinical trials (www.nci.nih.gov/search/clinical_trials) was also searched for listings of relevant open trials. The most recent literature search was performed in February 2003.

Inclusion Criteria

Articles were selected for inclusion in the systematic review of the evidence if they met the following criteria:

1. Studies that included patients with metastatic colorectal cancer in which raltitrexed was used and in which at least one outcome of interest (survival, progression-free survival, response rate, toxicity, symptom improvement and quality of life) was reported.
2. Randomized controlled trials were of primary interest but phase II studies were also retrieved.

NUMBER OF SOURCE DOCUMENTS

1998 Guideline

Three randomized controlled trials (RCTs) and one phase II study were reviewed.

2003 Update

Since the release of the guideline, two abstracts cited in the original guideline have been published in full, and one new randomized trial has been reported in abstract form. Three phase II studies, reported in abstract form only, have also been obtained.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Meta-Analysis of Summarized Patient Data
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

1998 Guideline

Data on survival time were not available to allow pooling using standard meta-analysis. Therefore. the median survival times of the patients in raltitrexed and 5 fluorouracil + leucovorin (5-FU+LV) treatment arms of the randomized controlled trials were pooled separately and weighted according to size of the treatment arms using the following formula:

weighted median survival = $[m_1n_1+m_2n_2+m_3n_3]/N$

where:

m=median survival within a treatment within a trial,

n=number of subjects within a treatment within a trial,

N=number of subjects within a treatment across trials.

Median survival times reported in the papers and abstracts were used. To estimate the overall effect on response rate of raltitrexed compared with 5-fluorouracil plus leucovorin (5-FU+ LV), the results of the randomized trials were pooled using Metaanalyst[0.988] software provided by Dr. Joseph Lau, Tufts New England Medical Center, Boston, MA. Results were expressed as odds ratios (with 95% confidence intervals [CI]) such that estimates <1.0 favor 5 fluorouracil + leucovorin (5-FU + LV) and >1.0 favor raltitrexed. Data were analyzed using the random effects model.

2003 Update
Survival data from one randomized controlled trial were added to the pooled analysis of response rates. The pooled median survival rates were also recalculated using the updated data.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Gastrointestinal Cancer Disease Site Group was most interested in addressing the observed inferior outcome with raltitrexed in one trial. Note was made of the fact that only one of the three studies showed a significant difference that was not in favor of raltitrexed. To address this, the results of the three randomized controlled trials (RCTs) were pooled. There was general agreement that raltitrexed appears to be as effective as 5-fluorouracil plus leucovorin (5-FU+LV) but is associated with lower rates of stomatitis and leukopenia.

Results of a Canadian cost-comparison study were reviewed. See the "Cost Analysis" field.

The DSG felt that raltitrexed is a safe and convenient alternative to 5-fluorouracil plus leucovorin in the treatment of symptomatic metastatic colorectal cancer. The use of raltitrexed should be considered where there are concerns about toxicity with standard 5-FU+LV, such as in older patients and females. Its use may also be preferred where the greater ease of administration is an advantage, such as for patients living a long distance from a treatment facility. Because of its convenient scheduling, raltitrexed may allow for more efficient use of institutional resources.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Results of a Canadian cost-comparison study were reviewed. This was a retrospective study of 60 patients from six institutions who participated in the North American trial. Patients were evaluated for pharmacy, nursing, physician and hospital costs. Overall health care costs were similar for patients treated with raltitrexed or 5-fluorouracil plus leucovorin (5-FU+LV). The higher drug acquisition costs of raltitrexed were offset by lower administration costs (pharmacy time and nursing administration time). In addition, there were lower hospitalization rates for patients treated with raltitrexed. Costs incurred directly by patients were significantly lower with raltitrexed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This describes the external review activities undertaken for the original guideline report.

Practitioner feedback was obtained through a mailed survey of 63 practitioners in Ontario. The survey consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey were reviewed by the Gastrointestinal Cancer Disease Site Group. The guidelines were approved by the Gastrointestinal Cancer Disease Site Group and the Practice Guidelines Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- For patients with previously untreated metastatic colorectal cancer in whom chemotherapy is indicated, a combination of 5-fluorouracil plus leucovorin (5-FU+LV) and irinotecan is now the standard treatment regimen.
- For patients with previously untreated metastatic colorectal cancer where monotherapy with fluoropyrimidines or other thymidylate synthase inhibitors (e.g. 5-FU+LV or capecitabine) appears appropriate, it is reasonable to offer raltitrexed as a therapeutic option. Suitable patients would include those for whom toxicity from 5-FU is a concern (such as patients who are over 60 years in age or women), or for whom the more convenient administration schedule of raltitrexed is important (one visit for raltitrexed every three weeks versus five daily visits with 5-FU every four weeks).
- At this time, there is insufficient evidence to make a recommendation for or against the use of raltitrexed in patients who progress on 5-FU+LV.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

1998 Guideline
One phase II trial and three randomized controlled trials (RCTs) were reviewed. The randomized controlled trials compared raltitrexed with 5-fluorouracil plus leucovorin (5-FU+LV).

2003 Update
Since the release of the guideline, two abstracts cited in the original guideline report have been published in full, and one new randomized trial has been reported in abstract form. Three phase II studies, reported in abstract form only, have also been obtained.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Four randomized controlled trials (RCTs) of raltitrexed compared with 5 fluorouracil (5-FU) plus leucovorin (LV) were reviewed. Results of two trials have been published in full and two in abstract form. Reports of all four RCTs presented data on time to disease progression; three of these trials demonstrated that median time to disease progression was significantly shorter for raltitrexed compared with 5-FU plus LV. The median survival times were not significantly different between raltitrexed and 5-FU plus LV in three of the RCTs, but one trial showed that median survival time was significantly shorter with raltitrexed. The weighted median survival time from four RCTs with published survival data was 10.2 months for raltitrexed compared with 11.2 months for 5-FU+LV. A pooled analysis of response rates using data from 1965 patients in four RCTs revealed an odds ratio of 0.95 (95% confidence interval, 0.76 to 1.19; p=0.66) demonstrating no significant difference in response rates between raltitrexed and 5-FU plus LV.

POTENTIAL HARMS

Data on toxicity from one of the randomized controlled trials (RCTs) indicate lower rates of leukopenia and stomatitis for raltitrexed compared with 5 fluorouracil (5-FU).

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Gastrointestinal Cancer Disease Site Group. Use of raltitrexed (Tomudex) in the management of metastatic colorectal cancer. Toronto (ON): Cancer Care Ontario (CCO); 2003 Feb [online update]. 16 p. (Practice guideline; no. 2-17). [22 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1998 May 22 (updated online 2003 Feb)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario, Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Gastrointestinal Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Gastrointestinal Cancer Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Use of raltitrexed (Tomudex) in the management of metastatic colorectal cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on August 19, 1999. The information was verified by the guideline developer as of September 17, 1999. This NGC summary was updated by ECRI on December 14, 2001 and most recently on July 21, 2003. The most recent information was verified by the guideline developer as of August 6, 2003.

COPYRIGHT STATEMENT

Date Modified: 11/8/2004